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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,724	10/19/2004	Mauro Marzi	2818-225	2529

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EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,724	MARZI ET AL.	
	Examiner	Art Unit	
	Charanjit S. Aulakh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1 page*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. According to a preliminary amendment filed on Oct. 19, 2004, the applicants have amended claims 6, 11-14 and 16.

2. Claims 1-18 are pending in the application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating lung tumor using instant compounds alone, does not reasonably provide enablement for treating every known tumor, parasitic or viral infections using instant compounds alone and/or in combination with any other drug . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following eight different factors (see Ex parte Foreman, 230 USPQ at 547; Wands, In re, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed: Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on atleast four of the above mentioned eight different factors such as quantity of experimentation

necessary, the amount of direction or guidance provided, presence of working examples, the state of the prior art and the breadth of claims.

The specification teaches cytotoxic activity of instant compounds using lung cancer cell line (NCI-H460) as shown on pages 14 and 15. Based on these teachings, the instant compounds will have utility in treating lung tumors. There is no teaching or data in the specification regarding inhibition of topoisomerase I with the instant compounds. There is no teaching either in the specification or prior art that topoisomerase I inhibitors are well known in the prior art to have therapeutic utility in treating every known tumor, parasitic or viral infections. There are no working examples present showing efficacy of instant compounds in vivo or in vitro models of all known tumors, parasitic or viral infections using instant compounds alone or in combination with any other drug. There is no teaching or guidance present to show how the instant compounds alone having cytotoxic effect in lung cancer cell line will have utility in treating every known tumor, parasitic or viral infection either alone or in combination with any other drug. The instant compounds of formulae (I) and (II) encompass several hundreds of thousands of compounds based on the values of variables R1, R2, R3, n and Z and therefore, in absence of such teachings, guidance and presence of working examples, it would require undue experimentation to demonstrate the effectiveness of instant compounds in known in vitro or in vivo models of all known tumors, parasitic or viral infections using instant compounds alone or in combination with thousands of other drugs and hence their utility for treating these disease conditions.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, formula (I), variable –OH is attached to the lactone ring via CH2 group. However, the specific compounds claimed in instant claim 4 are directed to homocamptothecin (-OH group is directly attached to the lactone ring) and furthermore, there is no teaching regarding preparing compounds of formula (I) where –OH group is attached via CH2 group to lactone ring in the instant process claims 6-9. Therefore, it is not clear whether the instant compounds of formula (I) is directed to compounds where –OH group is directly attached to the lactone ring or through –CH2 group? An appropriate correction is required.

In claims 6-9, the terms ----envisaged and Reformatsky reaction ---- are indefinite since their meanings are not clear. Also, the applicants are suggested to include the structures of the intermediate camptothecin and other intermediate derivatives in claims 6 to 9.

In claim 7, step a), line 2, ---7-(d-methoxymethyl)---- should read ----7-(dimethoxymethyl)----.

In claim 12, the term ---medicaments ---- is indefinite since it is not clear what type of medicine is being reffered here? And furthermore, what is being treated with the medicine?

In claims 14 and 15, the terms ---another active ingredient and anticancer agent ----- are indefinite since specific drugs or agents are not defined.

In claims 17 and 18, the terms ---tumors, parasitic or viral infections---- are indefinite since specific tumors and parasitic or viral infections are not defined.

Claims 11 and 16-18 provide for the use of a compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 11 and 16-18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 6, 7 and 12-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bigg (WO 97/00876, cited on applicants form 1449).

Bigg discloses novel camptothecin analogs, a process for preparing these compounds, pharmaceutical compositions containing these compounds and a method of treating tumors using these compounds. The compounds disclosed in examples 14 (see page 39) and 21 (see page 43) by Bigg anticipate the instant claims when R1 and R2 both represent H and R3 represents –OH or –OCH3 group in the instant compounds of formula (I).

10. Claim10 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Miyasaka (U.S.Patent 4,399,276).

Miyasaka discloses 7-substituted camptothecin derivatives. The compound, 7-dimethoxymethyl-camptothecin disclosed in example 9 (see col. 10, lines 36-37) by Miyasaka clearly anticipates the instant claim.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1-4 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penco (U.S.Patent 6,242,457) in view of Bom (J. Med. Chem., cited on applicants form 1449).

Penco discloses camptothecin derivatives having antitumor activity. The compounds of formula (I) (see col. 5, lines 1-67 as well as examples) disclosed by Penco are identical to the instant compounds of formula (I) except that they differ from the instant compounds in having a 6-membered lactone ring instead of 7- or 8-membered lactone ring fused to the tetracyclic ring. However, Bom teaches preparation of novel E-ring modified camptothecins and furthermore, teaches that expansion of the camptothecin E-ring to a 7-membered system (by insertion of a methylene spacer between the 20-OH functionality and the carboxyl moiety) enhances the solution stability of the agent while maintaining anticancer activity. Therefore, one skilled in the art would have been motivated to prepare the instant homocamptothecin derivatives by modifying 6-membered lactone ring of penco since Bom teaches enhanced solution stability of 7-membered lactone ring (see page 3018, second column).

14. Claims 1-4 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dallavalle (Expert Opin., cited on applicants form 1449).

Dallavalle discloses perspectives in camptothecin development. The lipophilic camptothecins (see page 840, 3.3) and specifically compound, 6 ST 1481 (gimatecan, see page 841) disclosed by Dallavalle identical to the instant compounds of formula (I) except it differs from the instant compounds in having a 6-membered lactone ring instead of 7- or 8-membered lactone ring fused to the tetracyclic ring. However,

Dallavalle teaches preparation of novel E-ring modified camptothecins and furthermore, teaches that expansion of the camptothecin E-ring to a 7-membered system (by insertion of a methylene spacer between the hydroxyl and the lactone moieties) enhances the plasma stability, decreased protein binding, potent topoisomerase I inhibition and high cytotoxic potency (see page 840, 3.4). Therefore, one skilled in the art would have been motivated to prepare the instant homocamptothecin derivatives by modifying 6-membered lactone ring since Dallavalle teaches enhanced plasma stability, decreased protein binding, potent topoisomerase I inhibition and high cytotoxic potency of homocamptothecins.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

C. S. Aulakh

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